

How often are parenteral anticoagulants administered by parents?

Abstract

Parenteral anticoagulants are a class of anticoagulants that need to be administered non-orally, usually by injection or infusion. There are a variety of such agents, but heparin reflects the most frequently used. Being alerted to an error in a prior publication in which the word “parenteral” was inadvertently replaced by the word “parental,” it became clear that even experienced authors make such errors, which could then remain undetected by reviewers and editors, thus leading to failure in correction of same before publication. Given this is likely to be a somewhat ongoing error, we undertook a PubMed search of the literature to identify that “parentally administered” anticoagulants, as well as “parental” administration of other compounds, seems to be evident throughout the literature. We hope this report acts to raise awareness and help avoid similar errors in the future.

way.¹ Other well-known parenterally administered anticoagulant agents include lepirudin, argatroban, and bivalirudin.

One of us was recently made aware of an error in a prior publication, where the word “parenteral” was inadvertently replaced by the word “parental” in some sections of the manuscript.² It is unclear if this error was introduced by the authors, or perhaps via Microsoft Word’s autocorrect feature. Nevertheless, either the authors or peer reviewers of this manuscript, or the journal’s editorial team, should have seen this error, inclusive of the proofing process, to enable the error to be corrected before publication. Given that even seasoned authors are capable of such an error, we felt it worthwhile to investigate how commonly such a simple linguistic mistake could occur in the current scientific literature. As noted, word processing programs such as Microsoft Word might not include the word “parenteral” in the basic dictionary, and if auto-correction is applied, could automatically use suggestions from the spell-checker to change the text, and as such “parenteral” might automatically be converted into “parental.” In this way, “parenterally administered anticoagulants” might become an inappropriate but still literally reasonable “parentally administered anticoagulants” (i.e., “administered by parents”).

1 | INTRODUCTION

Parenteral anticoagulants represent a class of drugs that need to be administered by a route other than the gastrointestinal tract; in other words, non-orally. The term parenteral is usually applied to drugs or other treatments given by injection and/or infusion. Moreover, the injection route can be subcutaneous, intramuscular, or intravenous. There are a variety of anticoagulant drugs that are administered parenterally, although heparin reflects the most common of these agents. Heparin can be administered as either unfractionated heparin, which may be administered by injection or infusion, or one of the low molecular weight heparins (LMWH), which are usually administered by injection, although studies on nasal delivery are also under

2 | HOW OFTEN ARE PARENTERAL ANTICOAGULANTS ADMINISTERED BY PARENTS?

To help assess this perplexing question, we initially undertook a simple PubMed search of the words “parental” and “heparin,” and uncovered that the error went beyond heparin, and so we undertook a second PubMed search using the term ((parental) AND (heparin OR anticoagulant OR enoxaparin OR clexane OR DTI OR “thrombin inhibitor” OR anticoagulant OR lepirudin OR argatroban OR bivalirudin)). This provided 1479 items, not all of which were relevant, and some of which used appropriate language, but which also highlighted that the error of “parental administration” was evidenced beyond the realm of anticoagulants. [Table 1](#) summarizes the errors that could be identified from this second search. In total, we identified 12 errors related to use of “parentally” administered “anticoagulants.”³⁻¹⁴

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Dedicated to our parents, in particular to Santa Maria Favaloro (1926-2022).

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TABLE 1 Summary of text related to inappropriate use of parental in simple PubMed search*

Citation	Text extract
<i>“Parental anticoagulants”</i>	
Kemper et al. ²	“After initial anticoagulation therapy regimens including fondaparinux, apixaban, and danaparoid failed, the patient was successfully treated with high-dose intravenous immunoglobulins in combination with parental anticoagulation therapy with argatroban.”
Gusdon et al. ³	“We will discuss oral antiplatelet medications and both IV and parental anticoagulants.”
Tadesse et al. ⁴	“Parental unfractionated heparin twice or three times per day was the most widely used thromboprophylaxis regimen.”
Tan et al. ⁵	“Sixthly, whenever possible, oral anticoagulation should be converted to parental heparin.”
Erikih ⁶	“During hospital stay patients in the new registry significantly more rarely received acetylsalicylic acid, parental anticoagulants, nitrates, and more often - dual antiplatelet therapy (DAPT), fondaparinux, statins.”
Fiore et al. ⁷	“Further studies are needed to establish the safety of NOAs in this clinical scenario. In the meanwhile, a viable alternative to VKAs, in order to prevent complications of VTE related to TB, may be represented by Low Molecular Weight Heparin (LMWH), notwithstanding the limitation of the parental route of administration.”
Lind et al. ⁸	“The aPTT does not correlate well with other tests that might be used to monitor parental DTI administration.”
Jia et al. ⁹	“rt-PA and parental anticoagulant were given to the patients in the treatment group while those in the control group received only parental anticoagulation.”
Kharchenko et al. ¹⁰	“Patients with bleeding prehospitally less frequently received aspirin and parenteral anticoagulants, while in hospital they were more frequently given diuretics and less frequently low molecular weight heparin while use of parental anticoagulants was similar in both groups.”
Desai et al. ¹¹	“A new class of medications, known as direct thrombin inhibitors (DTI), includes the parental agents lepirudin, argatroban and bivalirudin which have been approved by the FDA and the oral agents ximelagatran, melagatran and dabigatran.”
Kim et al. ¹²	“Heparin, one of the most potent anticoagulants widely used for the treatment and prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE), is currently available to patients only by parental administration.”
Hoffart et al. ¹³	“Owing to its lack of oral absorption, heparin has to be administered parenterally. However, parental administration has negative aspects such as multiple injections, possible infection, patient inconvenience, and high cost. Now, low molecular weight heparin (LMWH) is taking part in antithrombotic treatment and is proven to confer more advantages than unfractionated heparin.”
<i>“Parental nutrition”</i>	
Honinx et al. ¹⁴	“A cross-sectional study of deceased residents in nursing homes (2015) in six European countries: Belgium (Flanders), England, Finland, Italy, The Netherlands, and Poland. Potentially inappropriate treatments included enteral administration of nutrition, parental administration of nutrition, artificial fluids, resuscitation, artificial ventilation, blood transfusion, chemotherapy/radiotherapy, dialysis, surgery, antibiotics, statins, antidiabetics, new oral anticoagulants.”
Cole ¹⁵	“A 57-year-old morbidly obese male (150kg, BMI 42.5) presented to the emergency department with deep venous thromboses and pulmonary embolisms. He also had high output enterocutaneous fistula managed with an abdominal collection device, total parental nutrition therapy, and nil per os status.”
Hooda et al. ¹⁶	“The specific improvements for long-term use of this model are distal modifications of the catheters, postoperative treatment using parental nutrition and gut motility drug, prevention of infection of body cavity by further tunneling of catheters and blood flow probe cable, and use of ultrasonic blood flow probes and meter.”
Duerksen et al. ¹⁷	“A retrospective review of 47 malnourished AIDS patients started on home parental nutrition was performed.”
Squifflet et al. ¹⁸	“Finally, besides the general rules of recipient management common to kidney transplantation, pancreas transplantation further requires heparinization, insulin therapy and parental nutrition during the immediate postoperative period.”
<i>Other treatments</i>	
Salloum et al. ¹⁹	“She underwent 6 weeks of parental antibiotic therapy, 3 months of anticoagulation therapy and 7 days of steroids.”
Datta-Mannan et al. ²⁰	Our data indicate that the intrinsic PK/PD properties of native FST315 are poorly suited for acting as a parentally administered biotherapeutic with broad systemic effects.
Kleis et al. ²¹	“A 72-year-old white male developed bleeding from a right eye subconjunctival hemorrhage. The patient had been taking warfarin and, it was immediately discontinued. Two doses of 15mgs. Each of vitamin K given parentally reduced the prothrombin time, but not the oozing of blood which finally stopped after the administration of fresh frozen plasma.”

Interestingly, the search string ((parenteral) AND (heparin OR anticoagulant OR enoxaparin OR clexane OR DTI OR “thrombin inhibitor” OR anticoagulant OR lepirudin OR argatroban OR bivalirudin)) only identified 2865 items, and so only around twice the number using “parental” instead of “parenteral” ($n = 1479$).

In some respects, the outcome of the re-interpretation of the text, as actually written in the abstracts of the manuscripts with errors (Table 1), could be considered amusing, should a lighter view be taken. For example, Kim et al.¹² appeared to be adamant that “Heparin, one of the most potent anticoagulants widely used for the treatment and prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE), is currently available to patients only by parental administration.” Moreover, Hoffart et al.¹⁴ caution several negatives against parental administration, include “multiple injections, possible infection, patient inconvenience, and high cost.”

Some of the errors seem to be the result of translation from another language,^{7,10,11} or from authors for whom perhaps English is not the first language. However, quite a few were published in respected English language journals, including those that were hematology, or thrombosis and hemostasis related.^{3,9,13} Indeed, the earlier cited paper,² with errors in text, was published in a hematology journal. Interestingly, this particular paper did not appear in the PubMed search, because the term “parenteral” was correctly used in the abstract, but was instead incorrectly used as “parental” in the main text (primarily in one of the tables). This of course then identifies the limitation of using a PubMed search to ascertain the full extent of the problem, given that only abstracts (and not full texts) are available for search. Thus, our investigation probably represents an iceberg model, in which we can highlight a visible portion of the problem, but where the less visible submerged part of the iceberg is hidden to us. On the plus side, most of the identified manuscripts reflect historical publications, and so the true extent of the current problem, albeit unknown, may suggest improvement.

3 | BEYOND “PARENTALLY” ADMINISTERED ANTICOAGULANTS

Our PubMed search also identified another eight errors related to “parental” administration of other treatments, with the main error related to administration of “parental nutrition” (Table 1).¹⁵⁻¹⁹ Accordingly, we undertook a separate PubMed search of “parental nutrition” to identify 377 items, although this is only a small fraction (~1%) of the items (33708) identified using the appropriate term “parenteral nutrition.” Additional areas for errors included “parental antibiotic therapy,”²⁰ “parentally administered biotherapeutics,”²¹ and “parentally administered Vitamin K,”²² which was noted to reduce “the prothrombin time, but not the oozing of blood which finally stopped after the administration of fresh frozen plasma.” It was not noted if the fresh frozen plasma was also administered “parentally” in this 72-year-old patient.

4 | THE TERM “PARENTAL” IS OFTEN INTENDED

In contrast to occasional errors, the use of “parental” in the PubMed search was actually correct, including some occasions in which the word was used directly associated with the anticoagulant. For example, Oliveira et al.²³ mention that “The anticoagulant activity, determined by diverse assays and the in vivo antithrombotic and bleeding effects of the biosimilar version were confirmed as equal as of the parental enoxaparins.” In this paper, the authors were discussing biosimilars versus their “parental” version. As another example, Chen et al.²⁴ mention injection of a “parental hirulog” to test a “novel thrombin inhibitor, PTL060, comprising hirulog covalently linked to a synthetic myristoyl electrostatic switch to tether to cell membranes.” Thus, “parental hirulog” was used to define the original construct. Additional examples of usage in which “parental” was used in the correct context included other “parental” chain structures of heparin, “parental compounds,” “parental core structure,” and so on. In other cases, items were captured by the search in which DTI was used as a different abbreviation to “direct thrombin inhibitor” (e.g., “diffusion tensor imaging,” “drug targeting index”) and the term “parental” actually referred to parents (e.g., parental educational level, parental chromosomal aberrations, parental income), thereby explaining the context and inclusion in the captured PubMed items.

The reason we mention all this is because it seems quite plausible that authors sometimes intend to use “parental” and at other times intend to use the term “parenteral” in the context of anticoagulation (or other therapeutic) treatment.

5 | CONCLUSION

Our aim in this Forum piece is to bring this issue to broader attention, reminding all of us to be careful in our writing. Moreover, any such errors introduced by one of the authors should ideally then be captured by co-authors, reviewers, or journal editorial staff. In the interim, take care and be wary of the icebergs, as our search would only reflect usage in abstracts, and not main texts, and so the problem is anticipated to be greater than the search would suggest.

AUTHOR CONTRIBUTIONS

EJF wrote the original draft manuscript. All authors contributed to revise and approve the submission.

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CONFLICTS OF INTEREST

The authors state that they have no relevant conflicts of interest.

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